

C2 16. (amended) The method of claim 13 wherein the plant is selected from the group consisting of: *Zanthoxylum*, *Tinospora*, *Mahonia*, *Phellodendron*, *Aristolochia*, *Magnolia*, *Thalictrum*, *Coptis*, *Epimedium*, *Ranunculus*, *Sinomenium*, *Nandina*, *Manodora*, *Berberis*, *Fumaria*, *Pachygone*, *Dioscoreophyllum*, *Glaucium*, *Clematis*, *Aconitum* or *Cocculus*, *Xanthoxylum*, *Toddalia*, *Papaver*, *Hypecoum*, *Hylomecon*, *Prantl*, *Argemone*, *Eschscholtzia*, *Dicentra*, *Fagara*, *Symphoricarpos*, *Bocconia*, and *Xylocarpus*.

C3 26. (new) The method in claim 13 wherein the extract is neutralized to a pH between 4.5 - 7.0.

REMARKS

In response to the Office Action of May 21, 2002, claims 13 and 16 are amended, claims 17, 21, 24 and 25 are canceled and new claim 26 is added. Claims 13, 15, 16, 21, 24 and 25 were rejected under 35 U.S.C. § 102(b) as being anticipated by Southard *et al.*, U.S. Pat. No. 5,013,553 and claims 13, 15-17, 19 and 21-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Southard *et al.*, U.S. Pat. No. 5,013,553 in view of Mehlretter *et al.*, U.S. Pat. No. 2,715,627. Each of these rejections is discussed below.

Rejection under 35 U.S.C. § 102(b)

The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); Alco Standard Corp. v. Tennessee Valley Auth., 1 USPQ2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991) (citations omitted).

The Examiner has rejected claims 13, 15, 16, 21, 24 and 25 under 35 U.S.C. § 102(b) as being anticipated by Southard *et al.*, U.S. Pat. No. 5,013,553. The Examiner provides that these claims are drawn to a method for isolation and purification of an isoquinoline alkaloid via

extraction of a ground biomass of a plant with a solvent, neutralization and further concentration. These claims are further drawn to purification of the extract by a chromatographic method, wherein the plant is selected from a group of specific plant families and genus. The Examiner further provides that Southard *et al.* describe a method for isolating benzophenanthridine alkaloids, such as chelerythrine and sanguinaria from plants via extraction with a mineral acid/alcohol solvent, precipitation with a base and dissolution in water (neutralization), precipitation and drying (concentrating) and further applying to a silica gel column.

In response to this rejection, independent claim 13 has been amended to exclude benzophenanthridine alkaloids and dependent claims 24 and 25 have been canceled. As amended, claim 13 is now drawn to a method for the isolation and purification of aporphine alkaloids. Southard *et al.* do not disclose or suggest that their method can be extended to other alkaloids. As noted above, anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. The present invention, as amended, describes and claims a method for the isolation and purification of aporphine alkaloids. Applicant maintains that as amended the claims are not anticipated by the Southard *et al.* reference which teaches a method for extracting and isolating benzophenanthridine alkaloids. Applicant respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

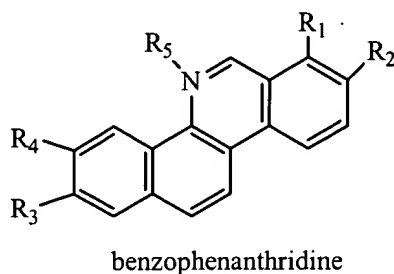
The Examiner has rejected claims 13, 15-17, 19 and 21-25 under 35 U.S.C. § 103(a), as being unpatentable over Southard *et al.* U.S. Pat. No. 5,013,553 in view of Mehlretter *et al.*, U.S. Pat. No. 2,715,627.

The Examiner bears the burden of establishing a prima facie case of obviousness. In determining obviousness, one must focus on Applicant's invention as a whole. Symbol Technologies Inc. v. Opticon Inc., 19 USPQ2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success. . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

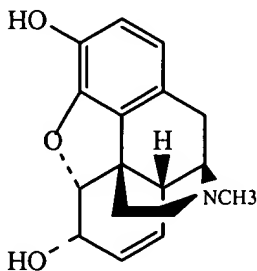
In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicant asserts that the cited references do not disclose or suggest the present invention, as amended, and therefore, do not render the present invention obvious.

As noted above, Southard *et al.* describe a method for isolating benzophenanthridine alkaloids, which have the following structure:



from plants via extraction with a mineral acid/alcohol solvent, precipitation with a base and dissolution in water (neutralization), precipitation and drying (concentrating) and further purification by silica gel column chromatography. Southard *et al.* do not disclose or suggest that their method can be extended to other alkaloids.

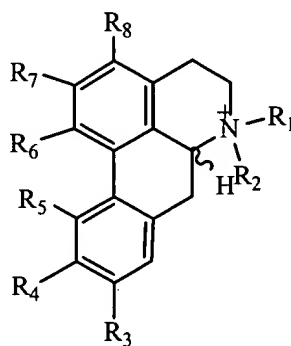
Mehlretter *et al.* disclose and claim a method for extracting opium alkaloids, specifically morphine and associated alkaloids from poppy. (Mehlretter *et al.*, col. 1, lines 21-25). The method described by Mehlretter *et al.* involves extraction with mineral acids, neutralization and evaporation. Mehlretter *et al.* also provides that the extract may be optionally purified by ion exchange chromatography (col. 2, lines 44-65), however, no examples of this technique are provided in the Specification. Morphine, is a phenanthrene alkaloid having the following structure:



Mehlretter *et al.* do not disclose or suggest that their method can be extended to other alkaloids.

The Examiner reasons that although these references do not state whether the methods described can be applied to other alkaloids, such as the aporphine alkaloids magnoflorine or laurifoline, "one of ordinary skill in the art would have had a reasonable expectation that alkaloids, having similar isoquinoline structures would have been extracted via the method proposed by Southard et al. (US 5013,553)." The Examiner further reasons that "[o]ne of ordinary skill in the art would have recognized that an extraction with an alcohol and/or acid would have produced a product containing aporphine alkaloids since alkaloids would have had similar polarities due to their phenolic rings." Additionally, the Examiner reasons that as evidenced by Mehlretter *et al.*, "alkaloids such as morphine, a phenanthrene alkaloid, is extracted with mineral acids, neutralization, evaporation and optional purification via column chromatography. (Col. 2, lines 44-65). From this the Examiner concludes that "although the structure of phenanthrene alkaloids are different, one of ordinary skill in the art would have reasonably appraised that the alkaloids of a plant (isoquinoline, aporphine, benzophenanthridine, etc.) could have been extracted with an acid or an alcohol to obtain a crude alkaloid product."

As noted above, the present invention, as amended, is limited to a method for the isolation and purification of aporphine alkaloids, which are a group of compounds having the following structure:



aporphine

Independent claim 13 has also been amended to exclude purification by absorption chromatography and claim 21 has been canceled. As amended, claim 13 is now limited to a chromatographic method of purification selected from ion exchange chromatography, reverse phase chromatography, size exclusion chromatography, ultra-filtration or a combination of two

or more of these methods. Support for claim 13 can be found in the Examples. Reverse phase chromatography and size exclusion chromatography are described in Example 1. Example 2 describes purification by nanofiltration and Example 4 describes purification by ion exchange chromatography. Additionally, new claim 26 has been added. Claim 26 is drawn to a method for the isolation and purification aporphine alkaloids wherein the extract is neutralized to a pH between 4.5 and 7.0. Support for new claim 26 can be found in the Specification on page 11, line 22, which describes one embodiment in which the extract is neutralized to 4.5-5.5 and on page 15, line 27, which describes neutralization of the extract to a pH of 7.0. This claim has been added to include a preferred embodiment of the invention.

As noted above, the Examiner concludes that although the structure of these three classes of alkaloids are different, one of ordinary skill in the art would have reasonably appraised that the alkaloids of a plant (isoquinoline, aporphine, benzophenanthridine, etc.) could have been extracted with an acid or an alcohol to obtain a crude alkaloid product. Applicant maintains, however, that this is not necessarily the case. As noted by Applicant in the Amendment and Remarks document submitted on February 20, 2002, the structure of morphine is very different from the structures of both aporphine and benzophenanthridine alkaloids. Furthermore, aporphine alkaloids contain a different ring skeleton than benzophenanthridine alkaloids. Additionally, the aromatic rings of aporphine alkaloids, usually contain a single or multiple phenolic hydroxyl groups. The differences in chemical structure of these classes of alkaloids, results in them having different physical properties. For example, aporphine alkaloids not only show basicity as typical of alkaloids, but also show acidity. As a result, aporphine alkaloids exhibit totally different solubility profiles and chromatographic behavior than benzophenanthridine and phenanthrene alkaloids. For example, the aporphine alkaloids of the current invention will not be precipitated by neutralization with basic solution as described for benzophenanthridine alkaloids (Southard *et al.*, col. 4, lines 50-55) and phenanthrene alkaloids (Mehlretter *et al.*, col. 3, Example 3). Additionally, absorption chromatography, such as alumina and silica gel chromatography can not be utilized to purify aporphine alkaloids due to irreversible absorption. However, Southard *et al.* describes the purification of benzophenanthridine alkaloids by silica gel chromatography. Thus, although one type of

Agreed by
Counsel
Not
3/2/02

chromatography is used to purify one class of alkaloids, it does not at all follow that other classes of alkaloids can be purified using that same method. As amended, claim 1 excludes absorption chromatography. Although Mehlretter *et al.* provide that phenanthrene alkaloids can be purified by ion exchange chromatography, no examples are provided. Furthermore, it does not necessarily follow that aporphine alkaloids can also be purified using this method. Mehlretter *et al.* do not describe or suggest that their method can be extended to other types of alkaloids. Applicant maintains that independent claim 13, as amended, is not obvious over either of the cited references, alone or in combination.

Regarding the remainder of the Examiners rejections, the Examiner reasons that a vat extractor appears to be similar to a large blender and one of ordinary skill in the art would have been motivated to have suitably blended the crude plant material/solvent. In response to this rejection, claim 17 has been canceled.

Claim 16 has been amended to exclude the plants referred to in the Southard *et al.* patent.

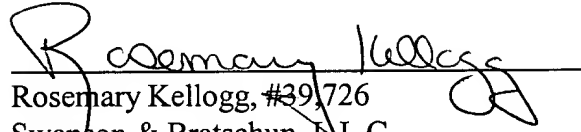
Regarding claim 19, which is drawn to extraction with a column extractor, the Examiner reasons that this apparatus is equivalent to mixing the crude plant material with solvent. Contrary to this conclusion, however a column extraction is a novel percolation process wherein fresh solvent is loaded at the top of the column and concentrated solution is eluted from the bottom of the column. A maximum concentration difference between solvent and biomass is always maintained, which significantly increases extraction efficiency. This process is totally different from manual blending or mixing solvent with biomass, in that several mixing/filtration batches must be performed on same biomass to reach same extraction yield as a column extraction.

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: August 21, 2002


Rosemary Kellogg, #39,726
Swanson & Bratschun, D.L.C.
1745 Shea Center Drive, Suite 330
Highlands Ranch, Colorado 80126
Telephone: (303) 268-0066
Facsimile: (303) 268-0065

cc: Qi Jia

S:\Client Folders\UniGen Pharmaceuticals\Uni15\Div\Uni.15 DIV OA 21.wpd

Marked up version showing changes to claims under 37 C.F.R. § 1.121(c)

13. (twice amended) A method for the isolation and purification of an [isoquinoline alkaloid selected from an] aporphine [or benzophenanthridine] alkaloid from a plant; said method comprising:

- (a) extraction of a ground biomass of a plant containing aporphine [or benzophenanthridine] alkaloids with a solvent;
- (b) neutralization and concentration of the neutralized extract; and
- (c) purification of said extract by a chromatographic method, wherein said chromatographic method is selected from the group consisting of ion exchange chromatography, reverse phase chromatography, size exclusion chromatography, ultra-filtration or a combination of two or more of these methods.

16. (amended) The method of claim 13 wherein the plant is selected from the group consisting of: *Zanthoxylum*, *Tinospora*, *Mahonia*, *Phellodendron*, *Aristolochia*, *Magnolia*, *Thalictrum*, *Coptis*, *Epimedium*, *Ranunculus*, *Sinomenium*, *Nandina*, *Manodora*, *Berberis*, *Fumaria*, [*Chelidonium*,] *Pachygone*, *Dioscoreophyllum*, *Glaucium*, *Clematis*, *Aconitum* or *Cocculus*, *Xanthoxylum*, *Toddalia*, *Papaver*, *Hypecoum*, *Hylomecon*, *Prantl*, *Argemone*, *Eschscholtzia*, [*Sanguinaria*, *Corydalis*,] *Dicentra*, *Fagara*, *Symphoricarpos*, *Bocconia*, and *Xylocarpus*[, and *Mocleaya*].